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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/360,199	07/23/1999	JACK GAULDIE	GDI-1	3800

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/360,199	Gauldie
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 26, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *29-32* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *29-32* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jul 23, 1999* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 17 on 9/23/02. Claims 1-28 were canceled and claims 29-32 were added as requested.

A supplementary amendment and Declaration of Dr. Jack Gauldie were received and entered as Paper No. 20 on 11/26/02.

A final rejection (Paper No. 19) in response to Paper No. 17 was completed on 11/25/02 and was mailed on 12/10/02. This action crossed in the mail with Applicant's supplemental response (Paper No. 20). Consequently the previous action Paper No. 19 is withdrawn in view the following Office Action.

Claims 29-32 are pending and under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and compositions for delivering a nucleic acid to gastrointestinal or genitourinary cells, wherein an immune response is induced against an antigen encoded and expressed by the nucleic acid, and while enabling for a method of providing a protective immune

response against HSV-2 infection, does not reasonably provide enablement for methods or compositions for treatment or prevention of diseases or disorders other than those caused by HSV-2, as broadly claimed, nor does it enable treatment of existing diseases or disorders as broadly claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

2. The factors to be considered in determining enablement are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Nature of the Invention and Breadth of the Claims

3. Claims 29-32 embrace methods of delivering to gastrointestinal or genitourinary cells in a recipient a "pharmaceutical composition" comprising an adenovirus encoding an antigen, wherein the methods result in the treatment or prevention of a pathologic condition by induction of an

immune response against the encoded antigen. For the purpose of examination under 35 USC 112, first paragraph, a "pharmaceutical composition" can be considered one which provides a therapeutic effect when delivered. Thus the claims embrace methods of therapy. Claims 30-31 limit the scope of the antigen to those of viruses, bacteria and mycobacteria. The scope of claim 29 is not so limited, and includes the treatment or prevention of any pathological condition, including *e.g.* cancers, diabetes, or atherosclerosis.

State of the art, Predictability of the art, and Level of skill in the art

4. Methods were known in the art prior to the filing date of the instant Application for employing mucolytic agents for the delivery of nucleic acids to gastrointestinal cells. For example, Henning et al prior art taught methods of delivering nucleic acids to intestinal cells, wherein the intestinal tissue was treated with a mucolytic agent. See e.g. WO/93/19660; US Patent 5,786,340, particularly claims 24 and 25; and US Patent 5,821,235, particularly claims 24 and 25. However, as discussed below, administration of nucleic acids to gastrointestinal and genitourinary tracts for treatment or prevention of the disease was highly unpredictable at the time of filing.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all

current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). In summary, at the time the invention was filed, the art gene therapy was highly unpredictable, without a single example of success in humans despite numerous attempts.

Chattergoon et al (FASEB J. 11: 753-763, 1997) set forth the state of the art of inducing therapeutic or preventative immune responses by delivery of antigen encoding nucleic acids. Although immune responses to several different antigens have been induced by delivery of naked DNA by intramuscular, intravenous, and intradermal administration routes, very few protective or therapeutic responses have been achieved relative to the unlimited scope embraced by claim 29, and the broad scope embraced by claim 30-32. Rather, the results generally indicated that, at the time of the invention, the field of genetic immunization was immature although promising. For

example, Chattergoon teaches that "DNA vaccines show promise for prophylactic immunization" for hepatitis virus (page 759, column 2, last sentence of first full paragraph), and results have provided "encouragement that DNA vaccines may be useful in meeting challenges inherent in developing malarial vaccines" (page 759, last sentence of second paragraph). With respect to tuberculosis, Chattergoon teaches that a single result of a protective immune response in a mouse challenge model indicates that "immunization with plasmid DNA-encoding mycobacterium antigen (or antigens) may provide a simple and efficient method for generating protective immunity." With respect to virus-induced cancers, Chattergoon teaches that "DNA immunization may prove useful in inducing protective immune responses prior to viral exposure." On the other hand, Irvine et al (J. Immunol. 156(1): 238-245, 1996) teach that "DNA immunization alone had little or no impact on the growth of established lung metastases", and that the delivery of cytokines in combination with the vaccine was required for protective effect. The specification does not account for any such modification of treatment. Thus the state of the art at the time of the invention was one of tentative optimism based on scattered successes, and did even those of the highest level of skill in the art could not practice therapeutic and protective immunization against any and all diseases and disorders as broadly claimed.

Examples and Guidance in the specification

5. The specification discloses no working example of genetic immunization. The specification discloses one working example which shows that the claimed method can be used to stimulate cytotoxic T cells. Recombinant adenovirus encoding Pym T antigen was administered

to mice intrarectally. Lymphocytes were harvested five days later, and shown to lyse specifically cells expressing Pym T antigen in vitro. While this example demonstrates that lymphocytes can be activated against antigens in vivo, but it does not demonstrate that the amount of activation is therapeutically relevant. The prior teaches that the results of CTL assays alone are insufficient to allow one to accurately predict the therapeutic effect of a given vaccine. In fact, it is well established in the art that in vitro assays of CTL activity cannot be considered to have relevance in vivo in the absence of confirmatory in vivo tests. For example, Lancki et al (1992) teaches that it is uncertain as to how CTL lysis of target cells in vitro "relates to the capacity of CTL to lyse such target cells in vivo", and notes that "[t]he role in vivo of such cytotoxic activity has not been determined." See abstract, and paragraph bridging pages 78 and 79. Furthermore, Bachmann et al (1994), in a comparison of in vivo and in vitro assays of T cell function teach that CTL responses readily detectable after in vitro restimulation may not be detected by any in vivo assay. Such responses lack biological relevance. "One should therefore be very cautious not to 'over-interpret' cytotoxicity found only by ^{51}Cr-release after secondary *in vitro* restimulation; without in vivo confirmation the results may be biologically irrelevant." To further highlight the unpredictability of the art, Wan (1997) teaches that the protective immune response obtained in vivo by inoculating mice with adenovirus modified to express Pym T antigen was highly dependent on the route of administration. Wan investigated several different routes, none of which was employed in the instant working examples.

Amount of experimentation required

6. In view of the unpredictability in the arts of gene therapy and genetic immunization, the lack of guidance regarding how to overcome the art-recognized barriers to success in gene therapy in general, and the lack of any in vivo working example of genetic immunization or gene therapy, one of skill in the art would have had to perform undue experimentation in order to use the claimed methods or composition for therapy or treatment of any disease or disorder.

Response to Arguments

Applicant's arguments filed 9/2/02 have been fully considered but they are not persuasive.

7. At page 3 of the response, Applicant asserts that the specification provides generous support and teachings that demonstrate the ability to generate a therapeutic immune response through the claimed methods, relying on Example 12 of the specification. This is unpersuasive for the reasons set forth above. That is, Example 12 uses a CTL assay an endpoint to measure immune response. However, it is well known in the art that without in vivo confirmation of an immune response, the results of CTL tests may lack biological relevance. See above. Applicant, while acknowledging at page 2 of Paper No.6 that the art is unpredictable, did not provide sufficient evidence or reasoning to support the position that a protective immune response would be generated against any antigen by the claimed methods or composition. Applicant noted that a declaration from Dr. Gauldie with accompanying relevant data was forthcoming. This declaration and accompanying supplemental response is considered below.

Applicant's arguments, and the Declaration of Dr. Gauldie, filed 11/26/02 have been fully considered but they are not persuasive.

The declaration of Dr. Gauldie provides evidence that mice immunized intrarectal administration of an adenoviral vector encoding HSV-2 gB8 were protected from HSV-2 challenge. This enabled scope is reflected in the statement of the rejection above. However, claim 29 broadly embraces treatment and prevention of *any* pathologic condition, including those that are not even caused by infections. It is also important to note that claims 29-31 require no relationship between the antigen of the adenoviral vector and the disease or disorder to be treated or prevented. Thus these claims read, for example, on methods of preventing diabetes with an adenoviral vector encoding Pym T antigen.

The declaration of Dr. Gauldie also provides evidence that mice immunized intrarectal administration of an adenoviral vector could protect mice from subsequent tumor challenge when tumor cells were delivered systemically, subcutaneously or intramucosally at the site of immunization. However, the tumor model used is not an art recognized model of disease. The tumor cells were modified to express a non-self antigen, chicken ovalbumin. As established above, the state of the art of genetic immunization against tumor antigens is unpredictable. So, it is not clear that a preventive immune response generated to an artificial tumor engineered to express a non-self antigen is enabling of methods of treating or preventing any natural pathological disorder with any naturally associated antigen.

In item 1 of the declaration, Dr. Gauldie considers the relevance of CTL assays to protective effect. Dr. Gauldie declares that "most data recently published show correlation" between CTL and protective effect. For support Dr.Gauldie relies on the tumor protection study discussed above, in which CTL assays showed evidence of an immune response. In view of the state of the art at the time of the invention, as set forth in the rejection, a single example of correlation between CTL assay results and protective effect cannot render all CTL assays indicative of protection. The position established in the rejection is that in vitro assays of CTL activity cannot be considered to have relevance in vivo in the absence of confirmatory in vivo tests. Neither the declaration nor the respnse presents evidence to the contrary.

For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henning (1993) and Wang (1997).

8. Henning teaches a method for delivering biologically active genes to the intestinal epithelium wherein the genes are expressed. See entire document, especially abstract. The nucleic acid may be delivered as an adenovirus (see page 9, lines 11-13), and may be delivered with a mucolytic agent (see page 11, lines 25-28; page 23, lines 1-11; and claims 61 and 62 on page 36).

Although Henning teaches that the method may be used to induce an immune response against an antigen encoded by the nucleic acid (see page 3, lines 19-21), Henning does not teach a working example of the induction of an immune response.

Wang teaches a method of delivering a naked nucleic acid to genitourinary and gastrointestinal cells in a chimpanzee. See abstract. When the method was used to deliver nucleic acids including retroviral sequences encoding HIV envelope proteins, an immune response against the envelope proteins was detected. See e.g. Fig. 2 on page 624.

Given the teachings Henning, it would have been obvious to one of ordinary skill in the art at the time of the invention to deliver to gastrointestinal or genitourinary cells a mucolytic agent and an adenoviral vector encoding a viral antigen. Given the teachings of Wang, one could have done so with a reasonable expectation of success of obtaining an immune response against the encoded antigen. Given the success of Wang in obtaining an immune response while using naked DNA, there is no reason to doubt that an immune response would not be obtained when using an adenoviral vector to deliver the antigen-encoding DNA. In fact, it would have been obvious to use the method of Henning to deliver an expression construct encoding the antigens of Wang.

One would have been motivated to do so in order to take advantage of the effect of the mucolytic agent of Henning.

It is noted that neither Wang nor Henning teach a working example of a therapeutic effect, however, while the claims embrace methods of therapy, the method steps do not require a therapeutic outcome. One of ordinary skill in the art would have had a reasonable expectation of inhibiting to some extent an infection by the virus of Wang because Wang teaches that neutralizing antibodies were produced in the method. See abstract, and page 623, column 2, first full paragraph. It is unpredictable as to whether such inhibition would provide a therapeutic effect, but because the claims do not explicitly require therapy, the combination of enablement and obviousness rejections set forth in this action is considered to be proper.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments, and the Declaration of Dr. Gauldie, filed 11/26/02 have been fully considered but they are not persuasive.

9. Applicant considers the art rejections at pages 3-6 of the response. Declarant considers the prior art at pages 4 and 5 of the declaration. The arguments generally are based on the position that the claimed invention represents a therapeutic vaccination approach. However, although the claims embrace methods of therapy, they do not explicitly require a therapeutic outcome. All that is required is an immune response specific to an encoded antigen. Applicant and Declarant have

failed to show that the cited art could not be properly combined to render obvious a method in which an adenovirus is delivered with a mucolytic agent to gastrointestinal cells, thereby resulting in an immune response to a foreign viral antigen encoded by the adenovirus.

While Applicant and Declarant appear to question whether or not the method of Wang produced an immune response (see page 5, item 4 of declaration and page 5 of the response), no evidence or reasoning is provided to suggest any other interpretation of the outcome observed by Wang.

Summary

Claims 29-32 are rejcted as not enabled for the full scope ofthe claims.

Claims 29-32 are rejected as embracing obvious embodiments.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441.

The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

Jeffrey Siew

JEFFREY SIEW
PRIMARY EXAMINER
2/23/03